

Manchineel keratoconjunctivitis

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Abstract

The Manchineel tree is an evergreen widely distributed in tropical regions. The toxic nature of Manchineel has been known since the early sixteenth century. Contact with its milky sap (latex) produces bullous dermatitis and acute keratoconjunctivitis. We identified 19 patients who had ocular injuries caused by Manchineel between 1985 and 1990 and were able to review 12. All of these patients had been treated by lavage, cycloplegia, and topical antibiotics. Of 20 episodes of exposure 14 affected both eyes. The cornea was damaged in 16 episodes, the extent varying from large corneal epithelial defects to superficial punctate keratitis. The epithelial changes had resolved in a mean period of 3.75 days (range 1 to 14 days). Two episodes caused stromal infiltration to appear and in one of these a stromal opacity remained 5 years later. The

final visual acuity was 6/9 or better in all eyes except in one patient who had visual impairment because of glaucoma. Our results suggest that despite the severity of the acute reaction, the long term visual prognosis is excellent in Manchineel keratoconjunctivitis. The historical and toxicological literature on Manchineel is reviewed.

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The Manchineel tree is found in the West Indies, Central America, the Bahamas, South America, and the west coast of Africa.¹ It has been described as the most toxic tree on the North American continent² and so in the United States it is allowed to grow only in the Everglades of Florida and the Virgin Islands National Park. The tree is capable of flourishing in a highly saline environment and is therefore usually found in coastal regions.³ It has an extensive root system which has led to planting in an effort to prevent coastal erosion.

This round-topped tree with dense foliage (Fig 1) grows to 20–40 feet in height and has a trunk 1–2 feet in diameter, covered by a smooth grey bark. The shiny, dark green leaves are broadly ovate in shape, finely serrated and 2–4 inches long. The green, inconspicuous flowers are arranged in stiff spikes. The fruit resembles the common green apple, being rounded, greenish-yellow, and 1–2 inches in diameter. The tree commonly forms dense thickets along beaches (Fig 2), but it can also exist in a stunted form on windward cliffs, where it may be no more than a few inches in height. When cut or broken, all parts of the plant exude a milky sap, or latex (Figs 3 and 4), which is strongly irritant to the skin and mucous membranes. It is also known that rainwater dropping through the canopy of the tree contains enough dissolved irritant to produce irritation^{4,5} and for this reason notices are often displayed on the tree in tourist areas warning against taking shelter under it in a rain shower.



Figure 1 A typical Manchineel tree.



Figure 2 A thicket of Manchineel trees growing in their typical habitat above the high-water mark along the coast.

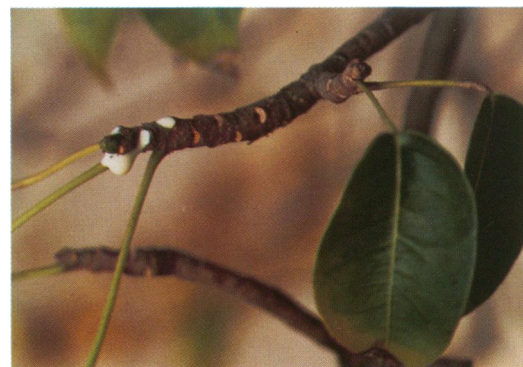
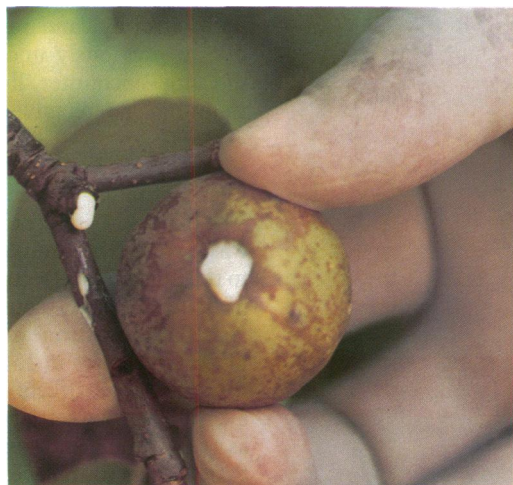


Figure 3 Latex exuding from the broken end of a branch.

Figure 4 Latex exuding from the fruit and stem.



The toxic properties of the Manchineel tree have been known for centuries to the native populations of the countries where it occurs. The warlike Caribs, who replaced the peaceful Arawaks as the aboriginal population of the Caribbean islands, apparently used the sap as an arrow poison, and it seems also to have had a medicinal role and one in 'trial by ordeal'.⁶ The scientific name, *Hippomane mancinella*, is derived from hippoman (horse poison) and mancinella (little apple) (Fig 4). Fatalities have been reported in humans and livestock eating the fruit and leaves.^{3,6} The main symptoms noted in systemic poisoning are lacrimation, salivation, vomiting, diarrhoea, and CNS depression leading to coma and death. It seems likely that these systemic effects are caused by physostigmine (see below). Another form of 'systemic' toxicity occurs when the fruit or leaves are eaten, producing pharyngeal oedema which has necessitated tracheostomy. The widespread, non-specific effects of Manchineel as an irritant are illustrated by the disastrous effects on the genitalia and perianal region by the unsuspecting use of the

leaves as toilet paper, or by children carrying the fruit in their swimming trunks.^{3,7}

Although the acute toxic effects of Manchineel on the human eye have been known for centuries in the countries where the tree grows,³ and have been described before, there have been no studies to determine the prognosis following exposure. We have therefore reviewed a series of patients to determine the long term sequelae.

Patients and methods

Patients with chemical burns caused by Manchineel were identified using the ward admissions record in the Department of Ophthalmology of the Queen Elizabeth Hospital (the only public hospital in Barbados) between 1985 and 1990. Details of patient age, sex, eye involved, visual acuity on presentation, extent of corneal involvement, treatment, and length of hospital stay were extracted. The patients were then invited to attend the clinic for further study. A more detailed history was then obtained to determine the reason for exposure and the part of the tree acting as the source of irritant. An ophthalmic examination was carried out to record the final visual acuity and look for abnormalities by slit-lamp biomicroscopy, endothelial specular reflection, and fluorescein staining.

Results

Nineteen patients were identified. Twelve of those were able to attend for review and for the remainder the only clinical details available were those extracted from the case records. Table 1 gives the details of the 19 patients. The mean age was 39.2 years (range 2–73). There was a strong male preponderance, with only one woman patient. One of the patients was a visitor to the island and had been ignorant of the tree, whereas the 18 Barbadian patients were aware of its dangers before exposure (in the youngest

Table 1 Clinical details of the 19 cases of Manchineel exposure

Patient	Age (years)	Sex	Mode of exposure	Source of toxin	Eye involved	Corneal involvement	Visual acuity (Snellen)		Time in hospital (days)	Time to review (months)	Visual acuity on review	
							R	L			R	L
1	32	M	OCC	Wood	Both	None	6/9	6/9	2	31	6/4	6/4
2	73	M	Gar	Wood	Right	Epi Def	6/60	6/9	5	16	HM	6/12
3	19	M	OCC	Wood	Left	Epi Def	6/6	6/4	1	2	6/4	6/4
4	27	F	OCC	Wood	Left	SPK	6/4	6/4	1	2	6/4	6/4
5	16	M	Shelter	Rain	Left	Epi Def	6/5	HM*	5	60	6/6	6/6
Sup stromal scar												
6	22	M	Shelter	Rain	Right	Epi Def	CF	6/5	5	18	6/4	6/4
7	2	M	ACC	Unknown	Both	Epi Defs	†	†	14	17		
8	28	M	Gar	Wood	Both	SPK	6/6	6/6				
9	44	M	OCC	Wood	Both	Epi Defs	6/24	6/24	4	7	6/4	6/4
Sup stromal opacity RE resolving with time												
10	20	M	ACC	Leaf	Left	Epi Def	6/5	6/5	1	7	6/4	6/4
11	28	M	OCC	Wood	Both	Epi Defs	6/18	6/18	3	36	6/4	6/4
12	19	M	ACC	Wood	Both	Epi Defs	6/18	6/18	3	36	6/4	6/4
13	46	M	Unknown	Unknown	Both	Epi Defs	6/24	6/36	2	DNA	DNA	DNA
14a	36	M	Gar	Wood	Both	Epi Defs	CF	CF	5	DNA	DNA	DNA
14b			Unknown	Unknown	Both	Epi Defs	CF	CF	4	0	6/9	6/9
15	25	M	Gar	Wood	Both	Epi Defs	6/9	6/6	4	7	6/5	6/6
16	24	M	Unknown	Unknown	Both	None	6/6	6/6	1	2	6/6	6/6
17	51	M	Unknown	Unknown	Both	None	6/9	6/9	Unknown	DNA	DNA	DNA
18	13	M	Unknown	Unknown	Both	SPK	6/9	6/12	Unknown	DNA	DNA	DNA
19	30	M	ACC	Leaf	Both	None	6/4	6/4	1	DNA	DNA	DNA

M=male; F=female; OCC=occupational; ACC=accidental; DNA=did not attend follow up; SPK=superficial punctate keratitis; Gar=gardening; Epi Def(s)=epithelial defect(s).

*VA reduced by advanced glaucoma.

†Formal assessment of acuity unsuccessful.



Figure 5 Skin ulcers and bilateral corneal epithelial defects 18 hours following contact with Manchineel sap (patient 9).

patient, the parents, who were supervising the child at the time of exposure, were aware of these). In all but one case, the patients had a single episode of exposure; case 14 had two episodes, recorded separately in the table. We were able to determine the circumstances of exposure in 15 of the 20 episodes. Nine episodes occurred while cutting the plant (five in the course of the patient's employment, and four during home maintenance). Four were caused by inadvertent contact with the tree and two by taking shelter beneath it in a rain shower. The part of the plant responsible for injury was ascertained in 14 episodes: the wood in 10 and the leaves in four (direct contact in two and filtering rain in two).

Of 20 episodes, 14 were bilateral. All eyes showed severe conjunctivitis and the cornea was involved in 16 episodes. Thirteen of those showed large corneal epithelial defects (Fig 5) and three showed superficial punctate epithelial keratitis. All patients had been treated by prompt lavage, cycloplegia to relieve pain, and instillation of antibiotic to prevent secondary infection while the cornea re-epithelialised. Steroids were not used in any case. The mean period to complete resolution of epithelial damage was 3.75 days (range 1–14). Two of our patients had stromal involvement: in one (patient 9), there was superficial stromal infiltrate in the acute phase (Fig 6) which disappeared in 3 weeks with return of visual acuity to 6/4. In another (patient 5), we noted a stromal scar persisting 5 years following the injury. (This patient had visual acuity of HM in the affected



Figure 6 Superficial stromal opacification, seen in the left eye of the patient in Figure 5, following healing of the epithelial defect (14 days following contact). In time this opacity was observed to diminish in size.

eye, but also had an afferent pupil defect, dense optic atrophy, and raised intraocular pressure due to previously undiagnosed glaucoma). We did not encounter limbal ischaemia, corneal thinning, or detectable intraocular inflammation.

Discussion

The historical literature dealing with Manchineel was reviewed by Lauter *et al* in 1952.⁶ References to the poisonous effects are found in the writings of Peter Martyr, court geographer to Queen Isabella, the patroness of Columbus, who wrote in *De Orbe Novo* in 1509 that 'even the shade of this fruit-tree affects the head and hurts the eyes'. The early settlers clearly regarded the tree as a deadly one, and frequently commented on its toxic effects to the eyes. Seeman, in his account of the voyage of *HMS Herald*, states that some of the ship's carpenters were temporarily blinded by the sap getting into their eyes while felling the trees.⁷ In 1673, Richard Ligon, a Barbados physician, wrote, 'the fellers as they cut them down are very careful of their eyes, and those that have cipers (handkerchiefs) put them over their faces, for if any of the sap fly into their eye they become blind for a month'.⁸ Admiral Horatio Nelson, while commanding a British expedition into Spanish Nicaragua, was poisoned by hostile Indians who had saturated spring water with Manchineel leaves.⁹ In 1943, Satulsky and Wirts⁹ reported 60 cases of facial dermatitis due to Manchineel exposure in troops on night manoeuvres in Panama, despite prior warning of the dangers of the plant by the US military in the *Manual of Jungle Warfare*. At least 50% of the soldiers were effectively blinded and required morphine analgesia before evacuation. It is of interest that many of those troops had not had direct contact with the tree; there had been a particularly heavy dew on the night in question, and the distribution of the skin lesions suggested that this had been the source of irritant. All of the men returned to active duty in 8 days, without sequelae. Harley¹⁰ reported four cases of acute keratoconjunctivitis among 18 cases of dermatitis venenata caused by Manchineel occurring in 1 year in Panama. Like Satulsky's cases, the dermatological lesions occurred mainly on the face, arms, trunk, and penis (contaminated during micturition).

These authors^{9,10} emphasised how rapidly the symptoms develop following exposure, with mild burning in a few minutes, progressing to severe burning, lacrimation, and blepharospasm within an hour. All of their patients recovered normal vision within 8 days, but Earle³ comments on persistent corneal ulceration in neglected cases. Harley¹⁰ also conducted limited experimental work on human skin and three rabbit eyes. He found, essentially, that irrigation of the rabbit eye 5 minutes after exposure reduced the healing time by one half, whereas irrigation at 15 minutes had no effect.

Manchineel is a member of the Euphorbiaceae (spurges), an extremely diverse family which is large enough, in the opinion of some botanists,¹¹ to merit reclassification as an order (the Euphorbiales). The family contains some 300 genera and 5000 species of trees, shrubs, and

herbs. Superficially these may bear little resemblance to one another but have in common the ovary, unisexual flowers, and fruit, which generally ripens 1 month after flowering; many have a milky sap.¹²

The Euphorbiaceae are widely distributed around the globe,¹³ although the majority are tropical. There are 18 species which occur in the British countryside,¹² all of which are rather inconspicuous herbs such as dog's mercury (*Mercurialis* spp) found on shady mountain rocks, and *Euphorbia portlandica*, which grows on coastal dunes in the south east of England. The non-botanical reader may well be more acquainted with the ornamental varieties grown in cultivation in this country, such as *Euphorbia pulcherrima* (poinsettia) and the *Codiaeum* species (croton), or with the common products of the Euphorbiaceae such as rubber (*Hevea brasiliensis*), castor oil (*Ricinus communis*), or tapioca (*Maritima* spp).

The topical Euphorbiaceae include other poisonous plants¹⁴⁻¹⁶ such as *Hura crepitans* (javelle, sandbox) the sap of which causes severe dermatitis, the *Sapium* species (one of those being used as a source of rubber in South America) and the common weed *Euphorbia lata* (Jamaican milkweed) which causes skin ulceration. Other poisonous Euphorbiaceae include African sandalwood (tombiti), yokes of which had to be discarded as they caused inflammation of necks of oxen, geor ('blind-your-eye'), and musine, which has been used in England for flooring and which some workmen find extremely irritant. Dermatitis, blepharitis, and keratoconjunctivitis have been described as occupational hazards in lumber workers and carpenters working with these woods, and much research has gone into the identification of the irritant chemicals. The main class responsible seems to be the terpenes, such as euphorbol.¹⁶ Duke-Elder also points out that some Euphorbiaceae are responsible for a violent iridocyclitis with hypopyon (*Tithymalus cyparissias* and *Euphorbia antiquorum*), but Manchineel had not been reported to do so.¹⁵

Schaeffer *et al*¹⁷ described the isolation of 2-hydro-4, 6-dimethoxy-acetophenone and a carotenoid substance from Manchineel leaves. Lauter and Foote¹⁸ suggested the presence of physostigmine. Neither study, however, investigated the toxicity of these substances. Rao¹⁹ carried out systemic fractionation of Manchineel latex based on toxicity to mice on intraperitoneal injection. He obtained a water soluble and an ether soluble fraction, both of which were toxic. He found eight fractions within the water soluble element, including the acetophenone described by Schaeffer, and a variety of the methyl derivatives of ellagic acid. The bulk of the water soluble fraction, however, consisted of substances which he named hippomanin A and B. Hippomanin A was later shown by the same author to be a 'crystalline tannin' which hydrolysed to glucose, gallic acid, and ellagic acid. The ether soluble fraction, meanwhile proved more toxic than the aqueous but was unstable and difficult to identify.

In 1984, Adolf and Hecker¹ reviewed the toxicological literature on the Euphorbiaceae

before investigation of Manchineel latex, and concluded from a chemotaxonomic point of view that physostigmine and hippomanin A would be unlikely candidates for skin irritants. They based this hypothesis on work on other toxic species of Euphorbiaceae, in which the irritant principals were found to be oxygenated diterpene esters of the tiglane, ingenane, or daphnane type (some of which had also been noted to be carcinogenic in mice). They separated Manchineel latex into a highly irritant hydrophilic fraction containing a large proportion of esters of 5 β -hydroxyresiniferonol-6 α , 7 α -oxide with 9, 11, and 14C chain fatty acids. The structure of one of these esters was found to be identical to huratoxin, the toxic principal of *Hura crepitans*. The non-irritants in the hydrophobic fraction could, however, be chemically activated to form irritant substances and were labelled 'cryptic irritants'. These were inactive triterpenes, a complex mixture of esters of tiglane and daphnane type (that is, the parent alcohols 12-deoxyphorbol and resiniferonol esterified with the even-numbered, unbranched fatty acids from C16 to C26). The authors conclude that owing to the presence of tumour promoting activity by these substances in mice, chronic contact with Manchineel products should be avoided.

It would seem, therefore, that Manchineel latex is a highly complex mixture of toxins. The most likely candidates for the production of keratoconjunctivitis would appear to be a mixture of oxygenated diterpene esters. These small, non-protein organic molecules are soluble in water, which explains why rainwater or dew can cause the syndrome of Manchineel-induced keratoconjunctivitis without direct contact with the tree. The precise mechanism of toxicity is unknown but seems likely to be a direct effect on the cells. Further *in vitro* studies on cornea using fractionated components of Manchineel sap would be needed to elucidate this.

Despite the complexity of the chemical toxicology and the severity of the acute reaction, our study suggests that the long term effects of Manchineel keratitis are not as drastic as historically believed. Unlike previous case reports, our patients consisted mainly of local people and in episodes of occupational exposure, the problem was not lack of awareness of the dangers of the plant, but inadequate eye protection.

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